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(21) International Application Number: PCT/GB90/00605 (22) International Filing Date: 20 April 1990 (20.04.90) (30) Priority data: 8909022.9 20 April 1989 (20.04.89) GB (71) Applicant (for all designated States except US): CORTECS LIMITED [GB/GB]; The Old Blue School, Isleworth, Middlesex TW7 6RL (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : STORY, Michael, John [AU/GB]; Elm Cottage, Greaves Lane, Threapwood, Nr. Malpas, Cheshire SY14 7AS (GB). BARNWELL, Ste- phen, John [GB/GB]; 30 Alun Crescent, Chester CH4 8HN (GB).		(74) Agents: SHEARD, Andrew, Gregory et al; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB). (81) Designated States: AT (European patent), AU, BE (Euro- + pean patent), CH (European patent), DE (European pa- tent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (Euro- pean patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS (57) Abstract <p>Pharmaceutically active agents are formulated with a bile salt and at least one additional component of bile. The bile salt and additional component may be provided as a naturally occurring bile mix, such as a methanolic extract of animal (for example, ox) bile. A lymphatic absorption promoter such as oleic acid or glycerol mono-oleate may also be present. Pharmaceuticals formulated in this way can benefit from enhanced bioavailability, particularly as hepatic first-pass metabolism is reduced. NSAIDs and cardiovascular agents are particularly suitable for formulation by means of the invention.</p>		

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1 PHARMACEUTICAL COMPOSITIONS

2
3 This invention relates to pharmaceutical compositions
4 which: promote the solubility of drugs which are only
5 poorly soluble in water; protect drugs when orally
6 administered, from the hostile acidic and enzymatic
7 environment of the stomach; protect the
8 gastrointestinal mucosa from the harmful effects of
9 such drugs as non-steroidal anti-inflammatory drugs
10 (NSAIDs); increase the bioavailability of drugs,
11 particularly those normally subject to significant
12 hepatic first-pass metabolism; and/or contain generally
13 inexpensive excipients. The invention also relates to
14 a method of formulating a pharmaceutically active agent
15 into a pharmaceutical composition and to methods of
16 administering drugs, as well as to the use of drugs and
17 certain other ingredients in the preparation of
18 pharmaceutically useful compositions.

19
20 It is in general known to formulate surfactants with
21 pharmaceutical agents for the purpose of solubilising
22 them as in, for example, EP-A-0179583. EP-A-0274870
23 teaches that NSAIDs, which are in general poorly water
24 soluble, can be administered, as well as solubilised,
25 as micelles and that this has advantages of (a)
26 potentially protecting the drug from the acidic and
27 enzymatic environment of the stomach and (b) protecting
28 the gastrointestinal mucosa from adverse effects of the
29 drug (such as gastrointestinal bleeding, which is
30 induced by NSAIDs including aspirin, indomethacin and
31 piroxicam).

1 Bile acids (or bile salts - the terms are used
2 interchangeably in this specification) are naturally
3 occurring surfactants. They are a group of compounds
4 with a common "backbone" structure based on cholanic
5 acid found in all mammals and higher vertebrates. The
6 detergent properties of bile acids are largely
7 determined by the number and orientation of hydroxyl
8 groups substituted onto a steroidal nucleus. Bile
9 acids may be mono-, di- or tri-hydroxylated; they
10 always contain a 3-alpha hydroxyl group, whereas the
11 other hydroxyl groups, most commonly found at C₆, C₇ or
12 C₁₂, may be positioned above (beta) or below (alpha)
13 the plane of the molecule. Many permutations of
14 hydroxyl configuration are possible, but certain
15 configurations are very much more common in nature than
16 others. In most animal species there is a recognised
17 pattern to the usual composition of the bile acids
18 found in the bile acid pool of individual animals.

19
20 Bile acids are synthesised in vivo from cholesterol in
21 the liver by hydroxylation and other modifications.
22 Virtually all bile acids found in the bile of mammals
23 and higher vertebrates are amidated at the C₂₄ position
24 with either taurine or glycine. The extent to which
25 various bile acids are amidated with either glycine or
26 taurine shows considerable variation between species
27 and depends on the availability of taurine as a
28 substrate for the conjugating enzyme.

29
30 Bile acids have various physiological functions.
31 Conjugated bile acids are secreted rapidly into the
32 bile by the liver, where they provide a means of
33 generating water flow by osmosis. It is in the

1 duodenum that bile acids perform their major role as
2 surfactants: they function to enhance the digestion and
3 absorption of dietary lipids and lipid soluble
4 vitamins. Bile acids also increase the action of
5 pancreatic lipases.

6
7 Miyazaki et al (Chem. Pharm. Bull. 27 (10) 2468-72
8 (1979)) have suggested that sodium deoxycholate and
9 sodium cholate enhance the dissolution of indomethacin
10 and phenylbutazone in pH 7.3 buffer at 37°C.

11
12 While in principle the addition of individual bile
13 salts to, for example, NSAIDs might take the place of
14 the particular surfactants disclosed in EP-A-0274870,
15 in practice, there are a number of problems with this
16 approach:

17
18 (a) Individual bile salts are generally too
19 expensive to be commercially useful;

20
21 (b) Individual bile salts have low (and variable)
22 solubilising powers on their own; and

23
24 (c) Certain bile salts promote absorption of some
25 drugs (Kimura et al (Chem. Pharm. Bull. 20
26 (8) 1656-62 (1972))) whereas some some
27 inhibit absorption (Yamaguchi et al (Chem.
28 Pharm. Bull. 34 (8) 3362-69 (1986))).

29
30 It has now been discovered that additional components
31 from bile can confer advantageous properties on
32 pharmaceutical compositions containing a

1. pharmaceutically active agent and a bile salt.
2 Solubilisation properties and/or drug delivery
3 characteristics may be improved.

4

5 According to a first aspect of the present invention,
6 there is provided a pharmaceutical composition
7 comprising a pharmaceutically active agent, a bile salt
8 and at least one additional component (other than
9 water) of bile.

10

11 The additional component, or one additional component,
12 may be a different bile salt. Alternatively or
13 additionally, the additional component, or one
14 additional component, may be a component of bile which
15 is not a bile salt and which may be a biliary lipid
16 such as a phospholipid. Biliary lipids are believed to
17 enhance micellisation and promote the lymphatic
18 absorption of lipids and lipid-soluble vitamins. It
19 is preferred to have more than one bile salt and one or
20 more other biliary components (such as biliary lipids)
21 present.

22

23 Native bile from most mammalian species contains large
24 quantities of the phospholipid phosphatidylcholine.
25 The phosphatidylcholine found in bile is of a highly
26 specific nature, quite different from that making up
27 the structural elements of the membranes of hepatocytes
28 and the cells surrounding the biliary tree.

29

30 The distinctive nature of biliary phosphatidylcholine
31 is determined by its constituent fatty acids: palmitic
32 acid (C:16) or palmitoleic acid (C16:1) being
33 esterified to the sn1-position, and either oleic acid

1 (C18:1), linoleic acid (C18:2) or linolenic acid
2 (C18:3) esterified to the sn2-position of the glycerol
3 backbone of the phospholipid. The exact distribution
4 of these fatty acid types in biliary
5 phosphatidylcholine does, however, vary considerably
6 between species.

7
8 The importance of these subclasses of
9 phosphatidylcholines, which are derived from a
10 metabolically compartmentalized synthetic pathway
11 destined to produce phosphatidylcholine for secretion
12 from hepatocytes, is their ability to form expanded
13 mixed micelles when combined with bile acids. Thus, by
14 acting as swelling amphiphiles they greatly enhance the
15 ability of bile acids to act as surfactants. For
16 example, bile acids have little tendency to solublize
17 non-polar lipids such as cholesterol in the absence of
18 phosphatidylcholine. This is important in vivo, where
19 biliary phosphatidylcholine is believed to aid the
20 incorporation of biliary cholesterol into bile acid
21 mixed micelles. Failure of this system to function
22 correctly probably leads to the formation of
23 cholesterol gallstones in man. In addition to their
24 function in bile, biliary phosphatidylcholines are
25 believed to enhance the micellization of lipids in the
26 duodenum. This function may be carried out by intact
27 phosphatidylcholine or equally as well by, and in
28 conjunction with, its natural degradation products such
29 as lysophosphatidylcholine and free fatty acids.

30
31 The inclusion of materials of this type in compositions
32 in accordance with the present invention appear greatly
33 to enhance solubilisation properties and/or drug

1 delivery characteristics observed when compared to
2 those in the studies using formulations containing
3 purified bile acids. The quantities of pure bile acids
4 required to produce pharmacologically useful effects
5 (see Kimura et al, Chem. Pharm. Bull, 20 (10), 2468-72
6 (1979); Yamaguchi et al, Chem. Pharm. Bull, 34, (8),
7 3362-69 (1986)) as active excipients in a drug delivery
8 system would preclude their incorporation in a
9 conventional dose form. Furthermore, their reliance on
10 very high concentrations of pure bile acids would rule
11 out their use on the basis of likely toxic side effects
12 when used repeatedly over long periods. In contrast,
13 when using the excipients used in the present
14 invention, the quantities administered remain
15 considerably below the levels of bile acids lost daily
16 from the host's bile acid pool. It is therefore
17 unlikely that the use of relatively small amounts of
18 bile acid of natural sources would be sufficient to
19 overload the systems used to handle the host's own
20 endogenous bile acids.

21
22 The bile salt and additional biliary component may
23 conveniently be provided by a naturally occurring mix
24 of bile components including bile salts such as animal
25 bile itself or an extract of bile. The naturally
26 occurring mix of bile components may be that naturally
27 occurring in any animal, preferably a domestic
28 livestock animal, as the bile components would be
29 available from the abattoir. Suitable animal sources
30 of bile components include oxen, pigs, sheep and other
31 animals. One suitable naturally occurring mixture of
32 bile components may be produced simply by evaporating
33 natural bile (for example ox bile) to dryness. Ox bile

1 extract, prepared in this way, is a dark
2 yellow-greenish powder containing a variety of bile
3 acids of which taurocholate is the most prevalent.
4 Bile acids themselves typically make up 50 to 60% of
5 the dry weight of the powder, bile pigments 5 to 10%,
6 and sulphated ash 10 to 20%; HPLC analysis indicates
7 that for ox bile total bile acids account for 69% of dry
8 weight, of which 17.5% is taurocholate, 14.1 % cholic
9 acid, 7.4% taurochenodeoxycholate, 6.1% taurodeoxy-
10 cholate, 1.7% tauroolithocholate and 1% minor bile
11 acids. In addition, there may also be small amounts of
12 cholesterol and phospholipid, as discussed above,
13 together with lipid and protein degradation products
14 formed in the manufacturing process.

15
16 A crude (but in some circumstances suitable) naturally
17 occurring mixture of bile components may be prepared
18 simply by drying bile from the abattoir. To achieve
19 this, the bile may be subjected to four processing
20 stages: evaporating, drying, milling and sieving. For
21 example, crude bile may be first reduced to a
22 concentrate. This may be done in one or more stages;
23 in one embodiment of the invention, the crude bile is
24 first reduced to a 50 to 60% concentrate, which is a
25 paste which is then transferred to a further
26 evaporation system to reduce it to a 70 to 80%
27 concentrate. The material may be finally dried to
28 substantially complete dryness, for example in a vacuum
29 oven over a period of about 4 days. The resulting
30 material has the consistency of brittle toffee and is
31 hygroscopic in nature. This may be milled, for example

1 into a powder. Milling can be carried out in a ball
2 mill, for example for 2 hours, after which it may be
3 sieved and packaged into appropriate containers.

4
5 It is generally preferred to use a somewhat more
6 refined bile salt mixture than is obtained as the
7 direct result of the above process. A refined extract
8 may be prepared by extraction with a simple organic
9 solvent such as an alcohol (for example C₁ to C₄
10 alcohols) or a ketone (for example, acetone). Methanol
11 is a preferred extraction solvent. An advantage of
12 refining the crude ox bile extract is that this step
13 removes certain mineral salts.

14
15 The pharmaceutically active agent and the mixture of
16 bile components are preferably intimately admixed
17 together. Such an intimate admixture may be produced
18 by grinding a solid preparation of the pharmaceutically
19 active agent with solid bile salt mixture, crude or
20 refined, as discussed above, to a very fine particle
21 size, for example less than 100 microns or even less
22 than 10 microns. It is however preferred to produce
23 the intimate admixture by dissolving the
24 pharmaceutically active agent and the bile salt mixture
25 in a common solvent and evaporating the solvent off.
26 It is particularly convenient if the same solvent is
27 used for this purpose as is used to refine the bile
28 components from a crude extract. As discussed above,
29 alcoholic solvents such as methanol are particularly
30 preferred. Other formulatary excipients, such as
31 enteric coating materials, may be found to be soluble
32 in the solvent of choice and, conversely, the solvent
33 will often be chosen with the solubility of other

1 excipients in mind. The solvent can be evaporated off
2 in a rotary evaporator, possibly under reduced pressure
3 conditions, for small scale preparations or in a drum
4 dryer on a larger scale.

5
6 Many of the advantages of the invention will be
7 realised with orally administerable compositions, and
8 such compositions are therefore preferred. Often, the
9 compositions will be substantially non-aqueous, by
10 which is meant containing less than 30, 20, 10 or even
11 5% water by weight.

12
13 It is preferred that pharmaceutical compositions in
14 accordance with the invention be produced in the form
15 of pellets, as these can provide a suitable basis for
16 further coating. Examples of functional types of
17 coating include: enteric coating to provide protection
18 of the contents from ionic disturbances in high acid
19 gastric media, as well as providing additional
20 protection of the stomach from the drug; sustained
21 release or controlled release coatings; and/or film
22 coating for rapid release preparations. Film coatings
23 for rapid release are preferred, as bile salts are
24 hygroscopic and uncoated pellets may be difficult to
25 handle if left standing, as they may have a tendency to
26 stick together to an unacceptable degree.

27
28 Pharmaceutical compositions in accordance with the
29 invention which are pellets may be prepared by coating
30 a solution (for example the preferred methanolic
31 solution) of the pharmaceutical active ingredient and
32 the bile salt mixture onto a suitable carrier such as
33 granulated sugar crystals. The crystals may be from

1 100 to 1000 microns in diameter, for example from 500
2 to 850 microns. The coating can be conveniently
3 achieved in a fluidised bed spray-coating machine, for
4 example using the Wurster configuration, or in a
5 semi-fluidised bed, for example using the bottom
6 rotating plate configuration, as in the
7 ROTOR-GRANULATOR device manufactured by Glatt or the
8 ROTO-PROCESSOR device manufactured by Aeromatic. (The
9 words ROTOR-GRANULATOR and ROTO-PROCESSOR are trade
10 marks. Top spraying is another suitable technique.

11
12 Other excipients may be present. For example,
13 plasticisers and/or binding agents may be used when
14 coating seed crystals or other matrix materials.
15 Suitable plasticisers include polyvinyl pyrrolidone
16 (povidone), hydroxypropyl methyl cellulose (HPMC),
17 propylene glycol, polyethylene glycol or hydroxypropyl
18 cellulose. Some of these materials can function as
19 additional solubilising agents, and the presence of
20 these or other solubilising agents is also within the
21 scope of the invention. Lecithin is a suitable lipid
22 solubilising agent, as are its naturally occurring
23 breakdown products, lysolecithin and free fatty acids.

1 A particularly preferred excipient is a lymphatic
2 absorbtion promoter. Examples of such materials, which
3 can be absorbed directly by enterocytes which surround
4 the gastrointestinal tract, will be known to those
5 skilled in the art. For the purposes of the present
6 invention, long chain (eg at least C₁₂ and preferably
7 C₁₂-C₂₄) fatty acids and their mono-esters, such as
8 with glycerol, are preferred. The acids and their
9 esterified derivatives may be saturated or (mono- or
10 poly-) unsaturated. Lymphatic absorbtion promoters
11 which have been found to perform well in the
12 compositions of the present invention include oleic
13 acid and glycerol mono-oleate.

14

15 The amount of lymphatic absorbtion promoter present
16 will depend on its nature and the nature of the
17 pharmaceutically active agent. In general, the
18 lymphatic absorbtion promoter may be present in an
19 amount of from 1 to 100% (w/w or v/w) based on the
20 amount of active agent, preferably from 5 to 50% and
21 typically from 10 to 35%.

22

23 Pharmaceutical compositions in accordance with the
24 invention may be found to be relatively soluble in
25 intestinal fluid, compared to the solubility in an
26 acidic aqueous environment, such as is found in the
27 stomach. This may be at least partly due to the
28 formation of a dark gummy mass which is a complex
29 formed by the components of the bile salt mixture in
30 acidic conditions. Although the dark gummy mass does
31 appear to dissolve in intestinal fluid, it takes longer

32

33

1 to do so than if it had not been exposed to acid, and
2 for this reason it is generally preferred that the
3 mixture of the pharmaceutically active agent and the
4 bile component mixture be protected from the acidic
5 stomach environment. This can be achieved by enteric
6 coating, as discussed above.

7
8 The mixture may be encapsulated in capsules such as
9 hard gelatin capsules, but any convenient capsules can
10 be used.

11
12 The present invention can be used to formulate
13 practically any pharmaceutically active agent
14 conveniently and relatively inexpensively. The
15 invention finds particular application in formulating
16 those pharmaceutically active agents which need
17 protection from the acidic environment of the stomach
18 and/or those from which the gastrointestinal mucosa
19 needs protection. Non-steroidal anti-inflammatory
20 drugs (NSAIDs) are examples of such pharmaceutically
21 active agents.

22
23 NSAIDs (or aspirin-like drugs - the two terms are used
24 interchangeably in this specification) can be
25 categorised conveniently into six structural groups.
26 First, there are the salicylic acids and esters
27 including aspirin, benorylate, aloxiprin, salsalate and
28 choline magnesium trisalicylate. Secondly, there are
29 the propionic acid derivatives, including ibuprofen,
30 naproxen, flurbiprofen, ketoprofen, fenoprofen,
31 fenbufen, benoxaprofen and suprofen. Thirdly, there
32 is the class of oxicams, including piroxicam.
33 Fourthly, acetic acid derivatives can be split into two

1 subclasses. Phenylacetic acids include diclofenac and
2 fenclofenac; carbo- and heterocyclic acetic acids
3 include indoles such as indomethacin and sulindac and
4 pyrroles such as tolmetin. Fifthly, there are the
5 pyrazolones which include oxyphenbutazone,
6 phenylbutazone, feprazone and azapropazone. Sixthly,
7 the fenamic acid derivatives include flufenamic acid
8 and mefenamic acid.

9
10 Of the above NSAIDs, there are some which can be
11 formulated particularly satisfactorily by means of the
12 present invention, particularly when using methanol as
13 a solvent for both the NSAID and the bile salt mixture.
14 These are: indomethacin, diclofenac, sulindac,
15 naproxen, piroxicam and mefenamic acid.

16
17 The present invention is not only useful for
18 formulating NSAIDs. In particular, it is useful for
19 formulating pharmaceutically active agents which are
20 subject to significant hepatic first-pass clearance, as
21 will now be discussed.

22
23 Administration of standard pharmaceutical preparations
24 via the oral route conventionally results in the
25 majority of the absorbed drug entering the hepatic
26 portal venous blood supply. Subsequently, this venous
27 system, draining most of the gastrointestinal tract,
28 passes directly through the liver without mixing with
29 the systemic blood supply. The consequence of this is
30 that many therapeutic agents conventionally undergo an
31 extensive first-pass clearance and metabolism, by means
32 of the liver's detoxification system, with the net
33 result that the material reaching the systemic blood

1 supply is very much reduced. In order to obtain
2 therapeutically effective concentrations in the
3 systemic circulation, relatively large doses have had
4 to be administered. A further problem is that the
5 nature and extent of the hepatic first-pass effect
6 displays considerable inter- and intra-subject
7 variation.

8
9 The implications of the first-pass effect are therefore
10 that wide variations in systemic blood levels of a
11 compound can be obtained from the same orally
12 administered dose leading to the possibility of
13 increased incidence of side-effects or toxic reaction
14 if the dose is too high, or even to a failure to
15 control symptoms at all if a very extensive first-pass
16 effect is present.

17
18 By means of the present invention, it may be possible
19 to avoid or reduce a hepatic first-pass clearance, as
20 there is evidence to suggest that pharmaceutical
21 compositions in accordance with the invention cause
22 redirection from the portal blood to the lymphatic
23 route of absorption from the gastrointestinal tract.
24 That the lymphatic system avoids the liver is a
25 function of its anatomy in that the major lymphatic
26 vessels, into which the gastrointestinal lymph system
27 drains, come together in the thoracic duct, which then
28 empties directly into the systemic circulation.

29
30 In a particularly preferred embodiment of the
31 invention, therefore, the pharmaceutically active agent
32 is one which is normally subject to significant hepatic

1 first-pass metabolism. Such pharmaceutically active
2 agents include, but are not restricted to, a number of
3 cardiovascular agents.

4
5 Cardiovascular agents which may in particular be
6 formulated by means of the present invention include
7 propranolol, metoprolol, verapamil, nifedipine and
8 diltiazem, either in the form of the free compound or,
9 where appropriate, as a salt. Atenolol and nadolol are
10 not subjected to first-pass metabolism but may
11 nevertheless be formulated with advantage in accordance
12 with the invention, for example in order to increase
13 their generally poor absorbtion.

14
15 Other pharmaceutically active agents which are subject
16 to a hepatic first-pass clearance to a significant
17 degree and/or which are poorly absorbed, or indeed any
18 other pharmaceutically active agent, may be formulated
19 by means of the present invention.

20
21 According to a second aspect of the present invention,
22 there is provided a process for the preparation of a
23 pharmaceutical composition, the process comprising
24 admixing a pharmaceutically active agent, a bile salt
25 and at least one additional component (other than
26 water) of bile. The bile salt and the additional
27 component(s) can be a premixture, such as by being part
28 of a naturally occurring mixture of bile components,
29 before the pharmaceutically active agent is mixed.

30
31 It will be appreciated that the invention can be used
32 in a method of chemotherapeutic treatment of a human or
33 animal patient, the method comprising the

1 administration of a composition in accordance with the
2 first aspect of the invention. The invention also
3 encompasses the use of a pharmaceutically active agent,
4 a bile salt and at least one additional component
5 (other than water) of bile (which may be provided by a
6 naturally occurring mixture of bile components) in the
7 preparation of a pharmaceutical composition.

8
9 The invention will now be illustrated by means of the
10 following preparation and examples.

11

12 Preparation 1 - Crude Ox Bile Extract

13

14 Crude bile, collected from the abattoir, is pumped into
15 a stainless steel tank and heated by steam coils and
16 reduced to a 50 to 60% concentrate. The resulting
17 paste is transferred to an open steam jacketed
18 evaporating pan system and reduced further to a 70 to
19 80% concentrate. Final drying of the material took
20 place in a vacuum oven over a period of about 4 days.
21 The resulting material had the consistency of brittle
22 toffee and was hygroscopic in nature. The solid
23 material was milled into a powder in a ball mill for 2
24 hours and then sieved and packaged into fibre-board
25 drums lined with polythene bags.

26

27 Preparation 2 - Crude Pig Bile Extract

28

29 Pig bile powder, which is light brown in colour, was
30 prepared in a similar fashion to ox bile powder, as
31 described in Preparation 1. Examples 28 to 46
32 illustrate the possible use of an alternative animal
33 source of biliary material for use in pharmaceutical

1 preparations. Pig bile has a different bile acid
2 composition to ox bile since it contains mainly
3 hyocholic acid instead of cholic acid.

4
5 Example 1

6
7 4.0g crude ox bile extract, as prepared in Preparation
8 1, was dissolved in 17.5g methanol. The solution was
9 heated with stirring and boiled for 10 minutes. After
10 allowing to cool, it was filtered through WHATMAN No. 4
11 filter paper. The methanol was made up to its original
12 volume and 1.0g indomethacin was added. After
13 dissolving the indomethacin with stirring, the solution
14 was evaporated in an EVAPOTEC Rotary Film Evaporater,
15 the water bath temperature being approximately 50°C and
16 a strong vacuum being maintained. The product crystals
17 were recovered and found to dissolve very rapidly and
18 completely in pH 6.8 phosphate buffer. (The words
19 WHATMAN and EVAPOTEC are trade marks.)

20
21 Example 2

22
23 4.0g of crude ox bile extract, as prepared in
24 Preparation 1, was dissolved in 15g methanol and the
25 solution was boiled for 30 minutes. After allowing to
26 stand, the solution was filtered and the filtrate was
27 made up to its original volume with methanol. 2.0g
28 indomethacin, 0.5g povidone and 0.5g hydroxypropyl
29 methylcellulose were dissolved in the resulting
30 solution before evaporating to dryness as described in
31 Example 1.

1 Example 3

2

3 4.0g of crude ox bile extract, as prepared in
4 Preparation 1, was dissolved in 25g methanol and the
5 solution was boiled for 30 minutes. After allowing to
6 stand, the solution was filtered and the filtrate was
7 made up to 100ml with methanol in order to achieve
8 dissolution of the 4.0g indomethacin and 0.8g povidone
9 which were added to it. The solution was evaporated to
10 dryness as described in Example 1. The crystalline
11 product dissolved easily in pH 6.8 buffer solution.

12

13 Example 4

14

15 The procedure of Example 3 was followed, but using the
16 following quantities of ingredients:

17

18	Crude ox bile extract powder	3.0g
19	Methanol	25g
20	Indomethacin	1.0g

21

22 A crystalline product was obtained.

23

24 Example 5

25

26 2.0g of crude ox bile extract, as prepared in Example
27 1, was dissolved in 10g methanol and the resulting
28 solution was boiled for 15 minutes before cooling and
29 filtering through a WHATMAN No. 4 filter. 4.0g of
30 naproxen acid was dissolved in the filtrate which was
31 made up to its original volume with methanol. The
32 solution was evaporated to dryness as described in

1 Example 1. A dense crystalline product was obtained
2 which was slowly soluble in pH 6.8 phosphate buffer
3 solution.

4
5 Example 6

6
7 4.0g of crude ox bile extract, as prepared in Example
8 1, was dissolved in 25g methanol and the resulting
9 solution was boiled for 30 minutes before cooling and
10 filtering through a WHATMAN No. 4 filter. 5.0g of
11 naproxen acid and 0.5g povidone were dissolved in the
12 filtrate which was made up to its original volume with
13 methanol. The solution was evaporated to dryness as
14 described in Example 1. A dense crystalline product
15 was obtained which was slowly soluble in pH 6.8
16 phosphate buffer solution.

17
18 Example 7

19
20 4.0g of crude ox bile extract, as prepared in Example
21 1, was dissolved in 25g methanol and the solution was
22 boiled for 30 minutes following cooling and filtering
23 through a WHATMAN No. 4 filter. 4.0g diclofenac acid
24 and 0.8g povidone were dissolved in the filtrate which
25 was taken up to 70ml with methanol. The solution was
26 evaporated to dryness as described in Example 1 and
27 fine soft crystals were produced which dissolved
28 rapidly and completely in pH 6.8 buffer solution.

1 Example 8

2

3 4.0g of crude ox bile extract, as prepared in Example
4 1, was dissolved in 25g methanol and the solution was
5 boiled for 30 minutes following cooling and filtering
6 through a WHATMAN No. 4 filter. 4.0g sulindac and 0.5g
7 povidone were dissolved in the filtrate which was taken
8 up to 100ml with methanol. The solution was evaporated
9 to dryness as described in Example 1 and fine soft
10 crystals were produced which dissolved rapidly and
11 completely in pH 6.8 buffer solution.

12

13 Example 9

14

15 462g of crude ox bile extract, as prepared in
16 Preparation 1, was dissolved in 1000g methanol. The
17 solution was warmed to 30°C and then allowed to stand
18 for one hour before being pressure filtered using
19 WHATMAN GF/D filters. 154g indomethacin and 62g
20 povidone were dissolved in the filtrate which was taken
21 to a total volume of 3.4 litres with methanol. A
22 UNI-GLATT fluidized bed, fitted with a WURSTER insert,
23 was used to coat 500g of granulated sugar sieved to
24 500-850 microns. The product temperature was
25 maintained at approximately 40°C and the coating rate
26 was approximately 450ml/hour. The resulting pellets
27 were sieved between 500 and 1400 microns to remove
28 fines and oversize, and they were then sprayed with a
29 film coat consisting of 25g of hydroxypropyl
30 methylcellulose dissolved in 300ml methanol. The
31 resulting pellets were essentially spherical with a
32 smooth glossy surface. They had a bulk density of
33 0.82g/ml and a potency of 126mg indomethacin per gram.

1 They readily dissolved in pH 6.8 buffer solution.
2 These pellets were filled into size "1" hard gelatin
3 capsules with a mean fill weight of 398mg, giving a
4 potency of 50mg indomethacin per capsule.

5
6 The same solution can be used to make pellets for
7 filling into Size "2" hard gelatin capsules, with a
8 potency of 25mg per capsule. The quantity of sucrose
9 core material is adjusted to give the require potency,
10 according to the following proportions:

11

12	Refined ox bile extract*	75
13	Indomethacin	25
14	Povidone	10
15	Hydroxypropyl methylcellulose	4
16	Sucrose (500-800 micron)	181
17		—
18		295mg

19

20 * Ox bile extract after methanolic extraction

21
22 Example 10A

23
24 75mg indomethacin capsules were prepared, suitable for
25 sustained release, using the following proportions of
26 materials:

27

28	Crude ox bile extract (Preparation 1)	150
29	Indomethacin	75
30	Povidone	20
31	Sucrose (500-800 micron)	115
32		—
33		360mg

1 This formulation allows for a 40mg sustained release
2 coat.

3

4 Example 10B

5

6 A lower ratio of crude ox bile extract/indomethacin was
7 tried, as follows:

8

9 300g of crude ox bile extract was dissolved in 1000g
10 methanol. The solution was boiled for 30 minutes, left
11 to stand overnight, and then pressure filtered. 300g
12 indomethacin and 60g povidone were dissolved in the
13 filtrate which had to be made up to 7.2 litres with
14 methanol so as to achieve full dissolution of the
15 indomethacin. The resulting solution was sprayed onto
16 340g sucrose (500-850 micron) in a UNI-GLATT fluidized
17 bed as described in Example 9. The resulting pellets
18 dissolved satisfactorily in pH 6.8 phosphate buffer
19 solution. Note that the solubility of indomethacin in
20 methanol decreases as the ratio of refined ox bile
21 extract/indomethacin decreases. The preferred
22 proportions given in Example 10A allow a higher
23 solubility of indomethacin in the spraying solution,
24 and hence a reduced volume of coating solution to be
25 sprayed.

26

27 Example 11

28

29 Pellets of naproxen were prepared according to the
30 methods described for Example 9, using the following
31 proportions of materials, but excluding the final film
32 coat:

23

1 Crude ox bile extract 100g
2 Methanol 600g

3

4 The solution was boiled for 30 minutes, allowed to
5 stand overnight and pressure filtered.

6

7 Naproxen acid 200g and
8 Povidone 15g

9

10 were then dissolved. The total solution volume was
11 made up to 2.6 litre with methanol and coated on to:

12

13 Sucrose (500-850 micron) 330g

14

15 This provides a partial coating. In order to achieve a
16 potency of 250mg per capsule, it would be necessary to
17 apply more coating solution to the above pellets, and
18 if using the UNI-GLATT fluidised bed to divide the
19 batch into two sub-batches, and then coat each
20 sub-batch until the required potency is achieved.

21

22 Example 12

23

24 Pellets of diclofenac were prepared using the following
25 proportions of materials and the methods of Example 9,
26 but without the final film coat:

27

28 Crude ox bile extract 200g
29 Methanol 1000g

30

31 Boil 30 minutes, stand overnight, pressure filter.

24

1 Diclofenac acid 200g

2 Povidone 40g

3

4 Dissolve in the filtrate with total volume being made
5 up to 2.0 litres with methanol. coat on to:

6

7 Sucrose (500-850 micron) 240g

8

9 The potency of the pellets is such that, after adding a
10 film coating or controlled release coating, 100mg of
11 diclofenac will be filled into a Size "1" gelatin
12 capsule.

13

14 Example 13

15

16 Pellets of sulindac were prepared according to the
17 methods described for Example 9, using the following
18 proportions of materials, but excluding the final film
19 coat:

20

21 Crude ox bile extract 200g

22 Methanol 1000g

23

24 Boil 30 minutes, stand overnight, pressure filter.

25

26 Sulindac 200g

27 Povidone 20g

28

29 Dissolve in the filtrate with the total volume being
30 taken up to 2.0 litre with methanol.

1 Coat on to:

2

3 Sucrose (500-850 micron) 340g

4

5 The resulting pellets, after having a final film
6 coating, could be filled in to Size "1" hard gelatin
7 capsules to give a potency per capsule of 100mg
8 sulindac. If 200mg capsules are required, the above
9 coating represents one-quarter of the coating solution
10 requirements. Splitting of the batch into two
11 sub-batches would be necessary when using the UNI-GLATT
12 fluidised bed after half the total coating solution has
13 been applied.

14

15 Example 14

16

17 Pellets of piroxicam were prepared according to the
18 methods described for Example 9, using the following
19 proportions of materials:

20

21	Crude ox bile extract	300g
22	Methanol	1000g

23

24 Boil 30 minutes, stand overnight, pressure filter.

25

26	Piroxicam	60g
27	Povidone	45g

28

29 Dissolve in the filtrate with the total volume being
30 taken up to 2.4 litre with methanol.

1 Coat on to:

2

3 Sucrose (500-850 micron) 435g

4

5 Apply final film coat of:

6

7 Hydroxypropyl methylcellulose 45g in
8 Methanol 500ml

9

10 The resulting pellets had a bulk density of 0.86 g/ml
11 and a potency such that 20mg piroxicam could be
12 achieved when the pellets were filled into Size "2"
13 capsules. The pellets readily dissolve in pH 6.8
14 phosphate buffer solution.

15

16 Example 15

17

18 5g oxide ox bile extract powder, as prepared in
19 Preparation 1, was added to 15ml of methanol and boiled
20 under reflux for 15 minutes on a heated magnetic
21 stirring plate. The cooled methanolic solution was
22 left overnight before being filtrated through a WHATMAN
23 No. 4 filter paper. The weight of methanol lost during
24 preparation was replaced and 1g of propranolol
25 hydrochloride dissolved. A fine greenish-yellow
26 crystalline product was easily recovered under rotary
27 evaporation containing an ox bile powder:propranolol
28 hydrochloride ratio of 5:1.

29

30 Example 16

31

32 The procedure described in Example 15 was followed,
33 using the following ingredients:

27

1 Crude ox bile extract powder 5.0g
2 Methanol 15.0g
3 Propranolol base 1.0g
4

5 A greenish-yellow crystalline product was formed.
6

7 Example 17
8

9 The procedure described in Example 15 was used, with
10 the following ingredients:
11

12 Crude ox bile extract powder 5.0g
13 Methanol 15.0g
14 Atenolol 1.0g
15

16 A greenish-yellow crystalline product was formed.
17

18 Example 18
19

20 The procedure outlined in Example 15 was used, with the
21 following ingredients:
22

23 Crude ox bile extract powder 5.0g
24 Methanol 15.0g
25 Metoprolol 1.0g
26

27 A crystalline product was obtained.
28

29 Example 19
30

31 The procedure outlined in Example 15 was used, with the
32 following ingredients:

1 Crude ox bile extract powder 5.0g
2 Methanol 15.0g
3 Diltiazem 1.0g

4
5 A crystalline product was obtained.

6
7 Example 20

8
9 The procedure outlined in Example 15 was used, with the
10 following ingredients:

11
12 Crude ox bile extract powder 5.0g
13 Methanol 15.0g
14 Verapamil 1.0g

15
16 A crystalline product was obtained.

17
18 Example 21

19
20 The procedure outlined in Example 15 was used, with the
21 following ingredients:

22
23 Crude ox bile extract powder 5.0g
24 Methanol 15.0g
25 Nifedipine 1.0g

26
27 A bright yellow crystalline product was formed.

28
29 Example 22

30
31 2g of crude ox bile extract powder, as prepared in
32 Preparation 1, was added to 15ml of methanol and boiled
33 under reflux for 15 minutes on a heated magnetic

1 stirring plate. The cooled methanolic solution was
2 allowed to stand overnight and then filtered through a
3 WHATMAN No. 4 filter paper. The weight of methanol was
4 restored to that present at the beginning of the
5 example and 1g of propranolol hydrochloride was
6 dissolved. A greenish-yellow crystalline product was
7 obtained upon removal of the methanol by rotary
8 evaporation under reduced pressure. The final ratio of
9 ox bile extract:propranolol was 2:1.

10

11 Example 23

12

13 The same procedure described in Example 22 was carried
14 out, using the ingredients listed below:

15

16	Crude ox bile extract powder	2.0g
17	Methanol	15.0g
18	Propranolol base	1.0g

19

20 A crystalline product was recovered.

21

22 Example 24

23

24 The same procedure described in Example 22 was carried
25 out, using the ingredients listed below:

26

27	Crude ox bile extract powder	2.0g
28	Methanol	15.0g
29	Atenolol	1.0g

30

31 Atenolol was a little slow to dissolve in the
32 methanolic solution, but still formed a crystalline
33 product.

1 Example 25

2

3 The same procedure described in Example 22 was carried
4 out, using the ingredients listed below:

5

6 Crude ox bile extract powder 2.0g

7 Methanol 15.0g

8 Diltiazem 1.0g

9

10 A crystalline product was formed.

11

12 Example 26

13

14 The same procedure described in Example 22 was carried
15 out, using the ingredients listed below:

16

17 Crude ox bile extract powder 2.0g

18 Methanol 15.0g

19 Verapamil 1.0g

20

21 A crystalline product was formed.

22

23 Example 27

24

25 The same procedure described in Example 22 was carried
26 out, using the ingredients listed below:

27

28 Crude ox bile extract powder 2.0g

29 Methanol 15.0g

30 Nifedipine 1.0g

31

32 A yellow crystalline product was formed.

1 Example 28

2

3 5.0g of pig bile extract powder, as prepared in
4 Preparation 2, was dissolved in 15ml of methanol and
5 boiled under reflux for 15 minutes on a heated magnetic
6 stirring plate. The cooled methanolic solution was
7 allowed to stand overnight and then filtered through a
8 WHATMAN No. 4 filter paper. The weight of methanol was
9 restored to 15.0g. 1g of naproxen was added and mixed
10 until dissolved. Upon removal of the methanol by
11 rotary evaporation, a light brown crystalline product
12 was formed.

13

14 Example 29

15

16 The same procedure described in Example 28 was carried
17 out using the ingredients listed below:

18

19	Pig bile extract powder	5.0g
20	Methanol	15.0g
21	Ketoprofen	1.0g

22

23 A yellow crystalline product was formed.

24

25 Example 30

26

27 The same procedure described in Example 28 was carried
28 out using the ingredients listed below:

29

30	Pig bile extract	5.0g
31	Methanol	15.0g
32	Diclofenac	1.0g

33

34 A yellow crystalline product was formed.

1 Example 31

2

3 The same procedure described in Example 28 was carried
4 out using the ingredients listed below:

5

6	Pig bile extract	5.0g
---	------------------	------

7	Methanol	15.0g
---	----------	-------

8	Sulindac	1.0g
---	----------	------

9

10 A bright yellow crystalline product was formed.

11

12. Example 32

13

14 The same procedure described in Example 28 was carried
15 out using the ingredients listed below:

16

17	Pig bile extract powder	5.0g
----	-------------------------	------

18	Methanol	15.0g
----	----------	-------

19	Indomethacin	1.0g
----	--------------	------

20

21 A yellow crystalline product was formed.

22

23. Example 33

24

25 The same procedure described in Example 28 was carried
26 out using the ingredients listed below:

27

28	Pig bile extract	5.0g
----	------------------	------

29	Methanol	15.0g
----	----------	-------

30	Flufeamic acid	1.0g
----	----------------	------

31

32 A yellow crystalline material was formed.

1 Example 34

2

3 The same procedure described in Example 28 was carried
4 out using the ingredients listed below:

5

6	Pig bile extract	5.0g
7	Methanol	15.0g
8	Ibuprofen	1.0g

9

10 A yellow crystalline product was formed.

11

12 Example 35

13

14 The same procedure described in Example 28 was carried
15 out using the ingredients listed below:

16

17	Pig bile extract	5.0g
18	Methanol	15.0g
19	Atenolol	1.0g

20

21 A yellow crystalline product was formed.

22

23 Example 36

24

25 The same procedure describe din Example 28 was carried
26 out using the ingredients listed below:

27

28	Pig bile extract	5.0g
29	Methanol	15.0g
30	Diltiazem HCl	1.0g

31

32 A yellow crystalline product was formed.

1 Example 37

2

3 The same procedure described in Example 28 was carried
4 out using the ingredients listed below:

5

6	Pig bile extract	5.0g
7	Methanol	15.0g
8	Diltiazem base	1.0g

9

10 A yellow crystalline product was formed.

11

12 Example 38

13

14 The same procedure described in Example 28 was carried
15 out using the ingredients listed below:

16

17	Pig bile extract	5.0g
18	Methanol	15.0g
19	Propranolol HCl	1.0g

20

21 A yellow crystalline product was formed.

22

23 Example 39

24

25 The same procedure described in Example 28 was carried
26 out using the ingredients listed below:

27

28	Pig bile extract	5.0g
29	Methanol	15.0g
30	Propranolol base	1.0g

31

32 A yellow crystalline product was formed.

1 Example 40

2
3 2.0g of pig bile extract was added to 15ml of methanol
4 and boiled under reflux for 15 minutes on a heated
5 magnetic stirring plate. The cooled methanolic
6 solution was allowed to stand overnight and filtered
7 through a WHATMAN No. 4 filter paper. The weight of
8 methanol was restored to that present at the beginning
9 of the example and 1g of naproxen was dissolved. A
10 light-brown crystalline product was recovered upon
11 removal of the methanol by rotary evaporation under
12 reduced pressure. The final ratio of pig bile
13 extract:naproxen was 2:1.

14

15 Example 41

16

17 The same procedure described in Example 40 was carried
18 out using the ingredients listed below:

19

20	Pig bile extract	2.0g
21	Methanol	15.0g
22	Ketoprofen	1.0g

23

24 A yellow crystalline product was formed.

25

26 Example 42

27

28 The same procedure described in Example 40 was carried
29 out using the ingredients listed below:

30

31

32	Pig bile extract	2.0g
33	Methanol	15.0g
34	Diclofenac	1.0g

35

36 A light-yellow crystalline product was recovered.

1 Example 43

2

3 The same procedure described in Example 40 was carried
4 out using the ingredients listed below:

5

6	Pig bile extract	2.0g
7	Methanol	15.0g
8	Sulindac	1.0g

9

10 A light-yellow crystalline product was recovered.

11

12 Example 44

13

14 The same procedure described in Example 40 was carried
15 out using the ingredients listed below:

16

17	Pig bile extract	2.0g
18	Methanol	15.0g
19	Indomethacin	1.0g

20

21 A yellow crystalline product was removed.

22

23 Example 45

24

25 The same procedure described in Example 40 was carried
26 out using the ingredients listed below:

27

28	Pig bile extract	2.0g
29	Methanol	15.0g
30	Flufenamic acid	1.0g

31

32 A yellow crystalline product was recovered.

1 Example 46

2

3 The same procedure described in Example 40 was carried
4 out using the ingredients listed below:

5

6	Pig bile extract	2.0g
7	Methanol	15.0g
8	Diltiazem HCl	1.0g

9

10 A yellow crystalline product was recovered.

11

12 Example 47 - Dissolution Study using Ox Bile Extract
13 Powder

14

15 The aim of the simple dissolution study was to obtain a
16 basic idea of how each formulation would behave under
17 the varying pH conditions experienced in the stomach
18 and duodenum. Three separate solutions were used,
19 U.S.P. intestinal fluid simulated pH 7.4 (no enzymes),
20 U.S.P. intestinal fluid simulated pH 1.27 (no enzymes),
21 and distilled water. Tests were carried out in small
22 glass bottles, containing either 120mg or 60mg of each
23 formulation depending upon whether the 5:1 or 2:1
24 excipient to active ratio material was used. Separate
25 dissolution studies were carried out at 25°C and 37°C
26 using 10ml of each test solution.

27

28 a) Solubility at pH 7.4

29

30 The following remained in a clear stable solution
31 in pH 7.4 buffer at both 25°C and 37°C.

- | | | | |
|---|-------|---------------------------|---------------|
| 1 | i) | Propranolol hydrochloride | (5:1) |
| 2 | ii) | Propranolol base | (5:1) |
| 3 | iii) | Atenolol | (5:1) |
| 4 | iv) | Diltiazem | (5:1) |
| 5 | v) | Metoprolol | (5:1) |
| 6 | vi) | Atenolol | (2:1 and 5:1) |
| 7 | vii) | Diltiazem | (2:1 and 5:1) |
| 8 | viii) | Metoprolol | (2:1 and 5:1) |

9

10 Verapamil (5:1) formed an emulsion but remained in
11 solution, while nifedipine (5:1) remained in
12 solution for a few minutes before forming a
13 precipitate and may therefore require higher
14 ratios of ox bile extract.

15

16 b) Solubility in Water

17

18 The following dissolved in water at 25°C and 37°C,
19 to form clear stable solutions:

20

- | | | | |
|----|------|------------|-------|
| 21 | i) | Atenolol | (5:1) |
| 22 | ii) | Diltiazem | (5:1) |
| 23 | iii) | Metoprolol | (5:1) |
| 24 | iv) | Atenolol | (2:1) |
| 25 | v) | Metoprolol | (2:1) |

26

27 c) Solubility at pH 1.27

28

29 None of the formulations formed a clear stable
30 solution at pH 1.27. However, the following
31 produced a clear solution over a gummy solid:

- | | | | |
|---|------|---------------------------|-------|
| 1 | i) | Propranolol hydrochloride | (5:1) |
| 2 | ii) | Verapamil | (2:1) |
| 3 | iii) | Metoprolol | (5:1) |
| 4 | | | |

5 The remaining formulations formed a cloudy
6 precipitate at pH 1.27; nevertheless, the
7 following also contained a gummy solid:

- | | | | |
|----|------|------------------|-------|
| 8 | | | |
| 9 | i) | Atenolol | (5:1) |
| 10 | ii) | Diltiazem | (5:1) |
| 11 | iii) | Propranolol base | (5:1) |
| 12 | iv) | Diltiazem | (2:1) |
| 13 | v) | Metoprolol | (2:1) |
| 14 | | | |

15 Example 48

16

17 Dissolution Studies using Pig Bile Extract Powder

18

19 A similar dissolution protocol was used to that
20 described in Example 28 except that formulations
21 contained pig bile extract powder.

22

23 a) Solubility at pH 7.4

24

25 The following remained in a clear stable solution
26 in pH 7.4 at both 25°C and 37°C.

27

28 NSAIDs

29

- | | | | |
|----|------|-----------------|-----------------|
| 30 | i) | Naproxen | (2:1) and (5:1) |
| 31 | ii) | Ketoprofen | (2:1) and (5:1) |
| 32 | iii) | Diclofenac | (2:1) and (5:1) |
| 33 | iv) | Sulindac | (2:1) and (5:1) |
| 34 | v) | Indomethacin | (2:1) and (5:1) |
| 35 | vi) | Flufenamic acid | (2:1) and (5:1) |
| 36 | vii) | Ibuprofen | (5:1) |

CARDIOVASCULAR AGENTS

- | | | |
|------|----------------|-----------------|
| i) | Atenolol | (5:1) |
| ii) | Diltiazem HCl | (2:1) and (5:1) |
| iii) | Diltiazem Base | (5:1) |

Propranolol HCl and propranolol base both dissolved slowly to form a hazy solution which did not precipitate out. Nifedapine and verapamil formulations did not show any apparent tendency to dissolve.

b) Solubility in Water

The following dissolved in water to form a clear stable solution at 25°C and 37°C.

- | | | |
|------|----------------|-----------------|
| i) | Ibuprofen | (5:1) |
| ii) | Atenolol | (5:1) |
| iii) | Diltiazem HCl | (2:1) and (5:1) |
| iv) | Diltiazem Base | (5:1) |

c) Solubility at pH 1.27

None of the formulations illustrated in the examples formed a clear stable solution at pH 1.27. However, the following produced a clear solution over a gummy solid:

- | | | |
|------|-----------------|-----------------|
| i) | Diltiazem HCl | (2:1) and (5:1) |
| ii) | Propranolol HCl | (5:1) |
| iii) | Verapamil | (2:1) and (5:1) |
| iv) | Diclofenac | (2:1) and (5:1) |
| v) | Sulindac | (2:1) and (5:1) |

1 Example 49 - Pharmacological Study

2

3 Experiments described in this example were designed to
4 investigate the effects of a mixture of bile acids on
5 the absorption of propranolol from the gastrointestinal
6 tract via the hepatic portal blood supply and the
7 lymphatic system. Standard surgical procedures were
8 used to enable samples of lymph, portal and systemic
9 blood to be collected under anaesthesia. Formulations
10 under test were administered in a solution dissolved in
11 20ml of pH 7.4 gastrointestinal buffer, via a
12 gastrointestinal catheter. The formulations were as
13 follows.

14

15 Formulation A - Ox bile extract and propranolol base,
16 in the ratio 5:1 by weight as prepared in Example 16.
17 The total dose was 12mg/kg body weight (equivalent dose
18 of propranolol 2mg/kg).

19

20 Formulation B - Ox bile extract and propranolol
21 hydrochloride, in the ratio 5:1 by weight as prepared
22 in Example 15. The total dose was 12mg/kg body weight
23 (equivalent dose of propranolol 2mg/kg).

24

25 Formulation C - Propranolol hydrochloride, 2mg/kg.

26

27 Lymph and blood samples were taken 5 minutes after
28 administration of the test solution and then at 15
29 minute intervals for 240 minutes. All samples were
30 collected in heparin to prevent coagulation. Blood
31 samples were centrifuged to remove red blood cells and
32 stored at 4°C. Plasma samples were extracted by passing
33 plasma through VAC-ELUTE mini-C₁₈ columns. Propranolol

1 was eluted from the columns with a mixture of
2 acetonitrile and 0.1M hydrochloric acid (1:1 v/v),
3 analysed by high pressure liquid chromatography and
4 quantified by comparison with authentic standards using
5 fluorescence detection.

6

7 The study was carried out using 4 pigs - A, B, C and D.
8 The formulation each pig received was as follows:

9

10 Pig A - Formulation A

11 Pig B - Formulation B

12 Pig C - Formulation C

13 Pig D - Formulation B

14

15 Pig D, in addition to Pig B, received formulation B
16 because of hepatic portal vein and lymphatic catheter
17 failure in Pig B. In this animal, the portal vein
18 cannula was defective throughout the study, whereas the
19 lymphatic cannula became obstructed about 45 minutes
20 after administration of the test solution.

21

22 The lymph flow for each pig was recorded before and
23 after administration of the test solutions. In
24 addition, the levels of propranolol found in the lymph
25 samples collected were measured. In order to ascertain
26 the overall effects of compositions in accordance with
27 the invention on lymphatic drug delivery, the
28 cumulative amount of propranolol secretion in the lymph
29 was derived from the lymph flow and the rate of
30 lymphatic secretion of propranolol. Table 1 below
31 shows the total amount of propranolol secreted into the
32 lymph after the time indicated.

TABLE 1

Pig	Amount of Propranol Secretion	Time
A	675 ng	240 minutes
B	1030 ng	60 minutes
C	300 ng	240 minutes
D	1025 ng	240 minutes

These results indicate that the formulations containing the bile salt mixtures are capable of increasing the total dose of propranol absorbed through the lymph by a factor of at least 2, and perhaps as much as 10 (if the rate of secretion in Pig B were to be extrapolated to 240 minutes). These results are illustrated in Figure 1.

The cumulative absorption of propranolol via the hepatic portal blood supply was also measured, and the results are shown in Figure 2. It should be noted that levels of propranolol are in relative units, as, under the protocol used, no measure of portal blood flow could be made.

It can be seen that the bile acid mixture generally delays the absorption of propranolol via the hepatic portal route, and in the case of Formulation B, they significantly reduce the extent of absorption via this pathway.

1 EXAMPLE 50

2

3 This example concerns the combination of bile acids,
4 propranolol HCl and the monoglyceride glycerol
5 mono-oleate.

6

7	Ox Bile Extract	78%
8	Propranolol HCl	14%
9	Glycerol mono-oleate	8%

10

11 The components were dissolved in excess (80%) alcoholic
12 solvent and then recrystallized as a green solid. This
13 material was packed into hard gelatin capsules which
14 were then enterically coated using hydroxypropyl
15 methylcellulose phthalate (HP55 by Shin-Etsu) in an
16 ethanol/water solvent system.

17

18 The composition of the enteric coating solution was:

19

20	HP55	6%
21	Ethanol	84.5%
22	Purified water	9.5%

23

24 The solution was applied to capsules, previously sealed
25 using a LICAPS Test Kit supplied by CAPSUGEL, in a
26 UNI-GLATT fluidized bed. (The words LICAPS, CAPSUGEL
27 and UNI-GLATT are trade marks.) The resulting batch
28 (D180) was subject to testing in human subjects.

1 EXAMPLE 51

2

3 This example concerns the use of the unsaturated fatty
4 acid oleic acid together with ox bile extract and
5 propranolol HCl.

6

7 Ox bile extract	67%
8 Propranolol HCl	13%
9 Oleic acid	20%

10

11 The components were mixed with and recrystallized from
12 excess (800%) alcoholic solution. The resulting green
13 crystalline solid was packed into hard gelatin capsules
14 and sealed using a LICAPS Test Kit supplied by
15 CAPSUGEL. The capsules were subsequently enteric
16 coated using hydroxypropyl methylcellulose phthalate
17 (HP55).

18

19 The enteric coating solution contained:

20

21 HP55	6%
22 Ethanol	84.5%
23 Purified water	9.5%

24

25 and was applied using a UNI-GLATT fluidized bed system.
26 The resulting batch (D179) was used in a human
27 bioavailability study.

1 EXAMPLE 52 - Pharmacological Study

2

3 Study Design

4

5 This clinical trial was a three way cross-over study
6 using nine subjects. The dose used in each case was
7 80mg of propranolol in the form of two separate
8 formulations in accordance with the invention: D179,
9 produced in Example 51 (Treatment A) and D180, produced
10 in Example 50 (Treatment B); or Inderal (ICI)
11 (Treatment C). Subjects were fitted with a venous
12 catheter and an initial blood sample taken. Further
13 blood samples were taken at 1h, 2h, 3h, 4h, 5h, 6h, 8h,
14 12h and 24h.

15

16 A brief medical record of the patients was taken,
17 together with an examination to ensure they were in
18 good health. History of smoking habits, alcohol and
19 caffeine consumption were recorded, together with age,
20 weight and height.

21

22 Blood samples were collected into EDTA Vacutainers
23 (trade mark) and plasma retained after centrifugation
24 for 15 minutes at 2500 rpm to remove red blood cells.
25 Plasma samples were immediately frozen and then stored
26 at -20°C until analysed using the HPLC method described
27 previously.

28

29 Results and Discussion

30

31 The plasma levels of propranolol determined in each
32 sample collected from the subjects during each
33 treatment were recorded against time. A comparison of

1 the area under the curve (AUC) achieved with each
2 treatment is listed in Table 1. The mean increase in
3 AUC of Treatment B over control was 35% while the mean
4 increase using Treatment A was 20%. A further
5 comparison between treatments was made on the basis of
6 peak plasma concentrations (See Table 2). The mean
7 increase in peak plasma propranolol levels was 56%
8 using Treatment B and 37% using Treatment A compared to
9 control Treatment C.

TABLE 1

A.U.C. (ng.h/ml)

	<u>D180</u>	<u>D179</u>	<u>Inderal</u>			
<u>Subject</u>	A	B	C	A/C	B/C	B/A
I	409	635	388	1.05	1.64	1.55
II	634	810	608	1.04	1.33	1.28
III	1143	1020	470	2.43	2.17	0.89
IV	551	902	698	0.79	1.29	1.64
V	375*	670	387	0.97	1.73	1.79
VI	399*	136	354	1.13	0.38	0.34
VII	242	355	272	0.89	1.31	1.47
VIII	1684	1321	1472	1.14	0.90	0.78
IX	368*	358*	264	1.39	1.36	0.97
Mean	645	690	546	1.20	1.35	1.19
s.d.	470	371	376	0.49	0.51	0.48
CV(%)	73	54	69	41	38	40

TABLE 2

Peak (ng/ml)

	<u>D180</u>	<u>D179</u>	<u>Inderal</u>			
<u>Subject</u>	A	B	C	A/C	B/C	B/A
I	62	86	46	1.35	1.87	1.39
II	93	138	67	1.39	2.06	1.48
III	178	134	57	3.12	2.35	0.75
IV	98	105	213	0.46	0.49	1.07
V	35	84	47	0.74	1.79	2.40
VI	58	58	56	1.04	1.04	1.00
VII	35	70	38	0.92	1.84	2.00
VIII	218	203	247	0.88	0.82	0.93
IX	69	50	28	2.46	1.79	0.72
Mean	94	103	89	1.37	1.56	1.30
s.d.	64	48	81	0.87	0.62	0.58
CV(%)	68	47	91	63	40	44

1 CLAIMS

2

3 1. A pharmaceutical composition comprising a
4 pharmaceutically active agent, a bile salt and at least
5 one additional component (other than water) of bile.

6

7 2. A composition as claimed in claim 1, wherein the
8 additional component is a different bile salt and/or a
9 biliary lipid.

10

11 3. A composition as claimed in claim 1, wherein the
12 bile salt and additional component are provided in a
13 naturally occurring mix of bile components.

14

15 4. A composition as claimed in claim 3, wherein the
16 naturally occurring mix of bile components comprises
17 animal bile or an extract of animal bile.

18

19 5. A composition as claimed in claim 4, wherein the
20 extract of bile is obtained by evaporating natural bile
21 to dryness.

22

23 6. A composition as claimed in claim 4, wherein the
24 extract of bile is prepared by extraction with an
25 organic solvent.

26

27 7. A composition as claimed in claim 6, wherein the
28 organic solvent is methanol.

29

30 8. A composition as claimed in claim 1, which is
31 substantially non-aqueous.

- 1 9. A composition as claimed in claim 1, comprising a
2 lymphatic absorbtion promoter.
3
- 4 10. A composition as claimed in claim 9, wherein the
5 lymphatic absorbtion promoter is oleic acid and/or
6 glycerol mono-oleate.
7
- 8 11. A composition as claimed in claim 1, wherein the
9 pharmaceutically active agent is a non-streoidal
10 anti-inflammatory drug.
11
- 12 12. A composition as claimed in claim 1, wherein the
13 pharmaceutically active agent is normally subject to
14 significant hepatic first-pass metabolism.
15
- 16 13. A composition as claimed in claim 1, wherein the
17 pharmaceutically active agent is a cardiovascular
18 agent.
19
- 20 14. A composition as claimed in claim 14, wherein the
21 cardiovascular agent is propranolol, metoprolol,
22 verapamil, nifedipine, diltiazem, atenolol and/or
23 nadolol.
24
- 25 15. A process for the preparation of a pharmaceutical
26 composition, the process comprising admixing a
27 pharmaceutically active agent, a bile salt and at least
28 one additional component (other than water) of bile.

1/2

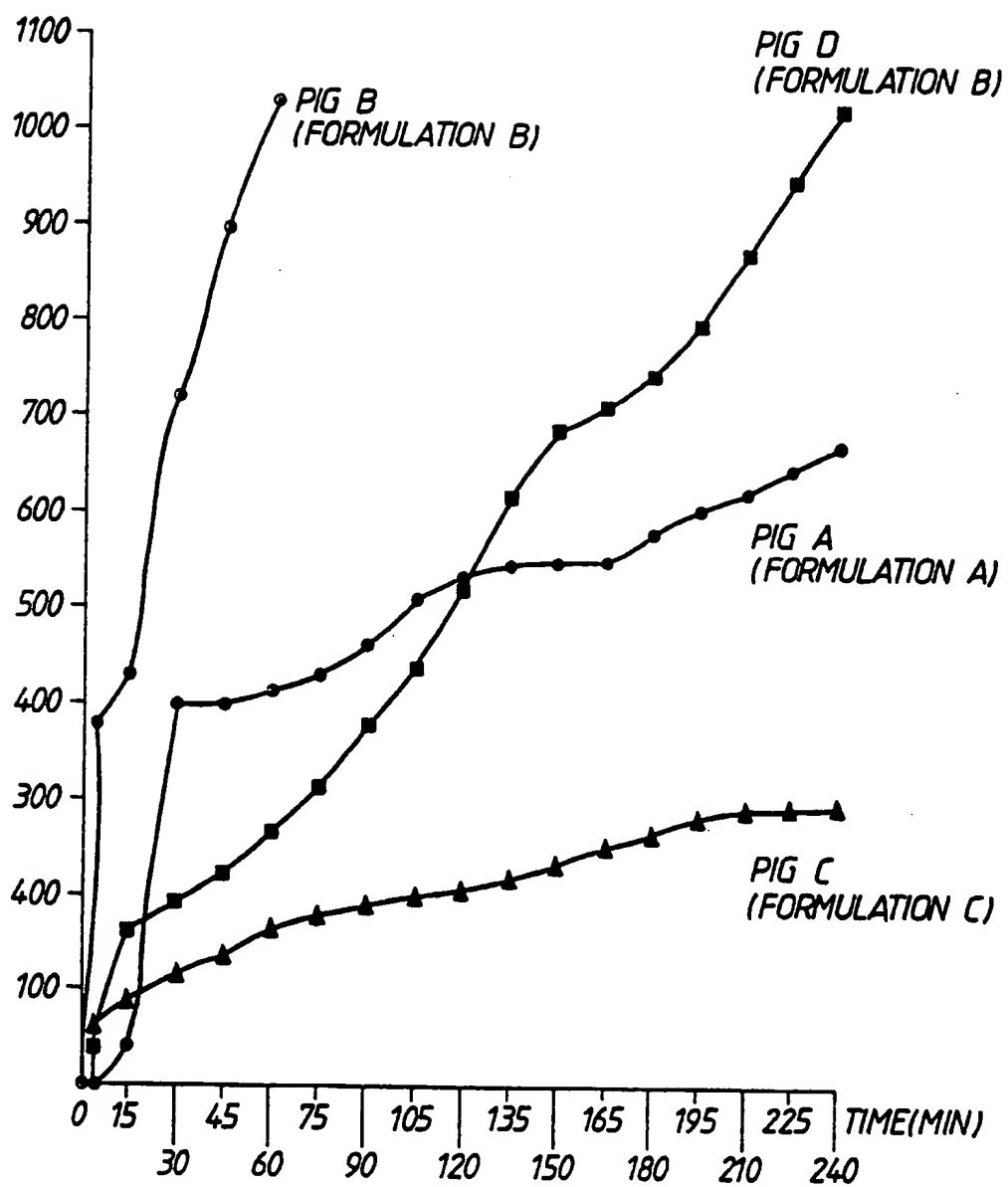


Fig.1.

SUBSTITUTE SHEET

2/2

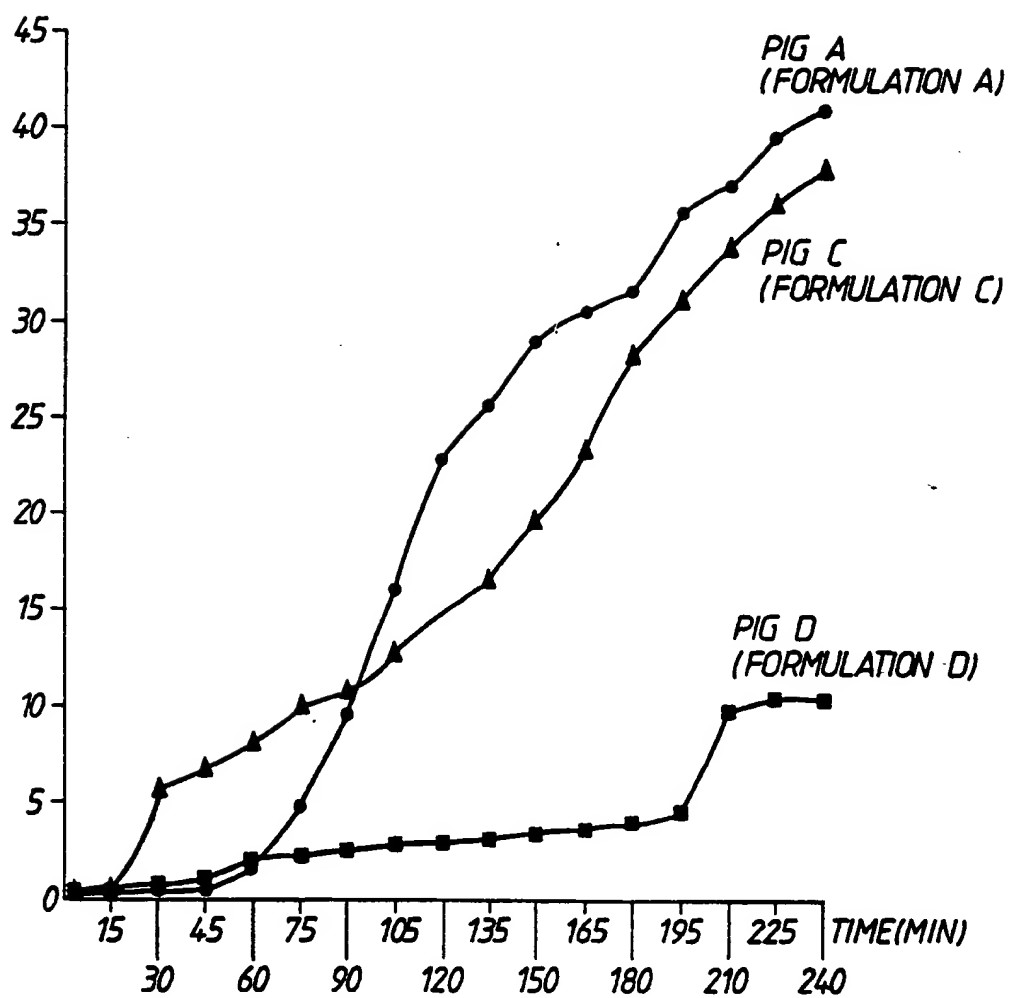
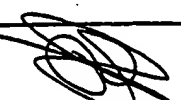


Fig.2.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/GB 90/00605**

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : A 61 K 35/413, 45/06, 47/12, //(A 61 K 35/413, 33:575, 31:405, 31:19, 31:135)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	Unlisted Drugs, volume 23, no. 3, March 1971 (Chatham, New Jersey, US), see page 41, K "QUINZYME" --	1-8
X	Unlisted Drugs, volume 26, no. 1, January 1974, (Chatham, New Jersey, US), see page 12, J "ZYMAZA" --	1-8
X	Unlisted Drugs, volume 26, no. 7, July 1974, (Chatham, New Jersey, US), see page 115, L "STO-ZYME" --	1-8
A	FR, A, 2427100 (KALI-CHEMIE PHARMA GmbH) 28 December 1979 see page 10, line 1 - page 12, line 20; claims 1-24 -- ./.	1-15
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁴</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
25th July 1990	14.08.90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	R.J. Eernisse 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, volume 102, no. 17, 29 April 1985, (Columbus, Ohio, US), M.R. Gasco et al.: "The influence of bile salts on the absorption in vitro and in vivo of propranolol", see page 12, abstract 142751u, & J. Pharm. Biomed. Anal. 1984, 2(3-4), 425-39 (Eng). see the abstract --	1-15
A	EP, A, 0179583 (MERCK & CO. INC.) 30 April 1986 see page 13, lines 15-18; example 4 cited in the application -----	1-15

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9000605
SA 36346

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 10/08/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2427100	28-12-79	NL-A- 7806048	04-12-79
EP-A- 0179583	30-04-86	AU-A- 4825285	10-04-86
		JP-A- 61091117	09-05-86

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82